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# Sex Differences in Presentation and Outcome Among Patients With Type 2 Diabetes and Coronary Artery Disease Treated With Contemporary Medical Therapy With or Without Prompt Revascularization

## A Report From the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes)

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**Objectives** This study evaluated differences in outcome among women and men enrolled in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial.

**Background** Women and men with coronary artery disease have different clinical presentations and outcomes that might be due to differences in management.

**Methods** We compared baseline variables, study interventions, and outcomes between women and men enrolled in the BARI 2D trial and randomized to aggressive medical therapy alone or aggressive medical therapy with prompt revascularization.

**Results** At enrollment, women were more likely than men to have angina (67% vs. 58%, $p < 0.01$) despite less disease on angiography (Myocardial Jeopardy Index 41 ± 24 vs. 46 ± 24, $p < 0.01$; number of significant lesions 2.3 ± 1.7 vs. 2.8 ± 1.8, $p < 0.01$). Over 5 years, no sex differences were observed in BARI 2D study outcomes after adjustment for difference in baseline variables (death/myocardial infarction/cerebrovascular accident: hazard ratio: 1.11, 99% confidence interval [CI]: 0.85 to 1.44). However, women reported more angina than men (adjusted odds ratio: 1.51, 99% CI: 1.21 to 1.89, $p < 0.0001$) and had lower scores for the Duke Activity Status Index (adjusted beta coefficient: −1.58, 99% CI: −2.84 to −0.32, $p < 0.01$).

**Conclusions** There were no sex differences in death, myocardial infarction, or cerebrovascular accident among patients enrolled in the BARI 2D trial. However, compared with men, women had more symptoms and less anatomic disease at baseline, with persistence of higher angina rates and lower DASI scores after 5 years of medical therapy with or without prompt revascularization. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D]; NCT00006305) (J Am Coll Cardiol 2013;61:1767–76) © 2013 by the American College of Cardiology Foundation

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**Abbreviations and Acronyms**

**CABG** = coronary artery bypass surgery
**CAD** = coronary artery disease
**CHF** = congestive heart failure
**CVA** = cerebrovascular accident
**DASI** = Duke Activity Status Index
**DM** = type 2 diabetes mellitus
**$HbA_{1c}$** = glycosylated hemoglobin
**LDL** = low-density lipoprotein
**MI** = myocardial infarction
**MJI** = Myocardial Jeopardy Index
**OR** = odds ratio
**PCI** = percutaneous coronary intervention
**QOL** = quality of life

Previous studies have reported differences in presenting clinical characteristics (1–16) and outcome (2–9) in women and men with coronary artery disease (CAD). Women with stable or unstable angina have been shown to have less extensive disease then men on coronary angiography (3,4,6,8,11,16) and are less aggressively treated than their male counterparts (3,5–7,10,11,17,18). These differences in clinical presentation and treatment will likely confound patient outcomes and therefore make a comparison of outcomes by sex more difficult. Some studies have shown that after adjustment for clinical and angiographic variables and differences in therapy provided, women and men had similar outcomes (7,8,13–15). Other studies report more restenosis or refractory ischemia (11,12) and worse overall outcomes in women compared with men (2–6,9). The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial data provide an opportunity to examine sex differences in outcome in a controlled population of patients with type 2 diabetes (DM) and CAD amenable to revascularization, who are all treated with similar protocol-mandated lifestyle and pharmaco-therapeutic management strategies.

## Methods

The BARI 2D trial was an international multicenter randomized clinical trial that evaluated the optimal treatment for patients with DM and documented CAD. A detailed description of the study design and patient population has been published previously (19–21). Between January 1, 2001, and March 31, 2005, a total of 2,368 participants were enrolled from 49 clinical sites in the United States, Canada, Brazil, Mexico, Czech Republic, and Austria. Enrollment criteria included a history of DM and angiographically documented CAD (defined as ≥50% stenosis of a major epicardial coronary artery and an abnormal stress test or ≥70% stenosis of a major epicardial artery with typical angina), involving at least 1 coronary vessel that was suitable for treatment with either aggressive medical therapy or elective revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). Patients were excluded if they had unstable symptoms necessitating revascularization, severe left main disease (≥50% stenosis), PCI, or CABG in the preceding 12 months or a history of chronic kidney disease with a serum creatinine above 2.0 mg/dl (176.8 μmol/l). Physicians were queried before randomization with regard to the recommended method of revascularization, and patients entered into either the PCI or CABG stratum. Patients were then randomized in a 2 × 2 factorial design to a strategy of prompt revascularization plus intensive medical therapy versus initial intensive medical therapy alone with clinically indicated revascularization for treatment of CAD. Subjects were randomly assigned to an insulin-providing or an insulin-sensitizing strategy for glycemic control. The primary endpoint of the BARI 2D trial was the rate of death from any cause. The principal secondary endpoint was a composite of death, myocardial infarction (MI), or stroke (cerebrovascular accident [CVA]) at 5 years of follow-up.

**Table 1** Baseline Demographic Data and Clinical Characteristics in Women and Men

| Characteristics | Women (n = 702) | Men (n = 1,666) | p Value |
|---|---|---|---|
| Age at entry, yrs | 62.9 ± 9.3 | 62.2 ± 8.7 | 0.11 |
| Race, ethnicity | | | <0.01 |
| White, non-Hispanic | 55.8% | 70.1% | |
| Black, non-Hispanic | 27.6% | 12.2% | |
| Hispanic | 12.7% | 12.5% | |
| Asian and others | 3.8% | 5.2% | |
| History of MI | 28.0% | 33.8% | <0.01 |
| History of hypertension | 87.1% | 80.6% | <0.01 |
| Prior revascularization | 22.4% | 24.1% | 0.37 |
| Diabetes duration, yrs | 12.2 ± 9.6 | 9.7 ± 8.1 | <0.01 |
| History of CHF | 7.8% | 6.2% | 0.14 |
| BMI (kg/m$^2$) | 32.8 ± 6.9 | 31.3 ± 5.5 | <0.01 |
| Neuropathy: clinical MNSI >2 | 45.7% | 52.2% | <0.01 |
| Intermittent claudication | 20.4% | 16.4% | 0.02 |
| History of cigarette smoking | 48.4% | 74.7% | <0.01 |
| Current smoker | 10.3% | 13.4% | |
| Angina | 66.5% | 58.2% | <0.01 |
| Stable CCS I–II | 63.7% | 73.1% | <0.01 |
| Stable CCS III–IV | 17.8% | 12.5% | |
| Unstable | 18.5% | 14.4% | |
| Angina equivalents | 72.6% | 60.1% | <0.01 |
| DASI | 14.1 ± 10.7 | 21.0 ± 14.0 | <0.01 |
| Self-Rated Health | 60.8 ± 20.7 | 65.1 ± 18.5 | <0.01 |
| LDL <100 mg/dl | 50.8% | 63.3% | <0.01 |
| Triglycerides <150 mg/dl | 52.1% | 49.9% | 0.34 |
| Blood pressure ≤130/80 mm Hg | 44.8% | 48.7% | 0.08 |
| $HbA_{1c}$ <7.0% | 32.3% | 42.7% | <0.01 |

Values are mean ± SD, %, or n.

BMI = body mass index; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; DASI = Duke Activity Status Index; $HbA_{1c}$ = glycosylated hemoglobin; LDL = low-density lipoprotein; MI = myocardial infarction; MSNI = Michigan Neuropathy Screening Instrument.

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**Table 2** Baseline Angiographic Data in Women and Men

| Angiographic Data | Women (n = 702) | Men (n = 1,666) | |
|---|---|---|---|
| Number of significant (>50%) lesions | 2.3 ± 1.7 | 2.8 ± 1.8 | <0.01 |
| Number of diseased region | | | <0.01 |
| 0–1 | 39.5% | 30.9% | |
| 2 | 36.5% | 35.6% | |
| 3 | 24.0% | 33.5% | |
| MJI | 41.0 ± 23.7 | 45.9 ± 24.2 | <0.01 |
| Category of MJI | | | <0.01 |
| 0%–20% | 22.3% | 16.8% | |
| 21%–50% | 45.5% | 42.2% | |
| 51%–100% | 32.2% | 41.1% | |
| Total occlusion | 31.1% | 45.3% | <0.01 |
| Significant proximal LAD (>50%) | 11.0% | 14.2% | 0.04 |
| LVEF <50% | 12.0% | 19.7% | <0.01 |
| LVEF, % | 58.8 ± 10.4 | 56.5 ± 11.1 | <0.01 |

Values are mean ± SD or %.
LAD = left anterior descending artery; LVEF = left ventricular ejection fraction; MJI = Myocardial Jeopardy Index.

Other secondary outcomes included congestive heart failure (CHF), the first subsequent revascularization, angina status, and quality of life (QOL). The subsequent revascularization was defined as the first clinically indicated revascularization among patients randomized to the aggressive medical therapy strategy or the second revascularization among patients randomized to the revascularization strategy. Angina status was reported at baseline, each month in the first 6 months of follow-up visits, and quarterly afterward. The QOL was assessed at baseline and at each annual follow-up visit. Self-administered questionnaires, including the Duke Activity Status Index (DASI) (22) and Self-Rated Health were used to assess the activity status and perceived health of a patient. The DASI is a 12-item index questionnaire assessing the ability of a patient to perform various activities without difficulty. Examples of activities assessed with DASI include walking a block on flat ground, climbing stairs, or doing housework. Each item is "weighted" such that the value for each question correlates with the metabolic cost of the activity described. The DASI scores range from 0 (worst—essentially unable to perform any activities independently) to 58.2 (best). Self-Rated Health is a single question administered to patients: "In general, would you say your health is excellent, very good, good, fair, or poor?" The responses are given numerical grades ranging from 0 (worst) to 100 (best).

In the current study, all comparisons were made between women and men. A descriptive analysis was performed for all baseline characteristics. Chi-square tests were performed to test general associations between sex and categorical characteristics. Two-sample *t* tests were conducted for the comparisons of means of continuous variables. The cumulative rate of event-type outcomes—including death; the composite of death, MI, or CVA; CHF; and the first subsequent revascularization—were compared with Kaplan-Meier estimators. The comparisons were further assessed by multivariable Cox regression models, adjusting for randomization strategy of CAD (medical therapy vs. revascularization) and glycemic control (insulin sensitizing vs. insulin providing); intended revascularization (PCI or CABG stratum); and relevant baseline characteristics including age, race, enrollment site, history of MI, hypertension, angina status, duration of DM, smoking history, number of left ventricular diseased regions, and abnormal left ventricular ejection fraction (<50%). Other repeated measured outcomes included angina status and QOL over 5 years of follow-up, where the follow-up year was coded as a categorical variable. The annual prevalence of angina was compared with chi-square test. Furthermore, a longitudinal logistic model with an approach of generalized estimating equations was constructed to estimate the overall odds ratio (OR) comparing women with men, adjusted for follow-up year, randomization strategies, intended revascularization strata, baseline angina status, and other baseline characteristics as listed in the preceding text. A similar approach was used to estimate the OR for achieving guideline recommended targets of low-density lipoprotein (LDL) <100 mg/dl, glycosylated hemoglobin ($HbA_{1c}$) <7% and blood pressure ≤130/80 mm Hg over 5 years of follow-up. The annual score of DASI and Self-Rated Health were com-

**Table 3** Characteristics of Revascularization Procedures in Subjects Randomized to Revascularization in Women and Men

| | Initial PCI Procedures | | |
|---|---|---|---|
| | Women (n = 244) | Men (n = 521) | p Value |
| Residual MJI | | | 0.46 |
| 0% | 44% | 38% | |
| 1%–20% | 27% | 27% | |
| 21%–50% | 24% | 28% | |
| 51%–100% | 5% | 6% | |
| Number of intended lesions | 1.52 ± 0.87 | 1.53 ± 0.79 | 0.89 |
| Number of successful lesions | 1.46 ± 0.83 | 1.45 ± 0.79 | 0.90 |
| Presence of lesion complications (%) | 5.7% | 5.6% | 0.92 |
| | **Initial CABG Procedures** | | |
| | Women (n = 87) | Men (n = 260) | p Value |
| Residual MJI | | | 0.59 |
| 0% | 33% | 30% | |
| 1%–20% | 30% | 36% | |
| 21%–50% | 36% | 32% | |
| 51%–100% | 1% | 3% | |
| Number of conduits grafted | 2.67 ± 0.9 | 2.92 ± 0.9 | 0.03 |
| Number of grafts | 2.55 ± 0.9 | 2.88 ± 0.9 | <0.01 |
| Number of arterial conduits | 1.09 ± 0.5 | 1.25 ± 0.6 | 0.04 |
| Intended lesions not grafted (%) | 17% | 13% | 0.33 |

Values are % or mean ± SD.
CABG = Coronary Artery Bypass Graft Surgery; MJI = Myocardial Jeopardy Index; PCI = Percutaneous Coronary Intervention.

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**Table 4** Medication and Lifestyle Management at Baseline and in Follow-Up in Women and Men

| | Follow-Up Year | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | | 1-Yr | | | 2-Yr | | |
| | Women (n = 702) | Men (n = 1,666) | p Value | Women (n = 632) | Men (n = 1,517) | p Value | Women (n = 606) | Men (n = 1,441) | p Value |
| Medication | | | | | | | | | |
| Beta-blocker | 75% | 72% | 0.22 | 87% | 86% | 0.56 | 87% | 85% | 0.16 |
| Calcium channel blocker | 34% | 30% | 0.09 | 40% | 37% | 0.16 | 37% | 38% | 0.90 |
| ACE or ARB | 76% | 78% | 0.37 | 92% | 89% | 0.10 | 92% | 90% | 0.13 |
| Nonsublingual nitrate | 35% | 30% | <0.01 | 27% | 23% | 0.09 | 26% | 19% | <0.01 |
| Diuretic | 50% | 34% | <0.01 | 68% | 48% | <0.01 | 72% | 54% | <0.01 |
| Any antiplatelet | 88% | 91% | 0.07 | 92% | 93% | 0.36 | 94% | 96% | 0.14 |
| Statin | 73% | 76% | 0.14 | 93% | 94% | 0.21 | 93% | 94% | 0.39 |
| Lifestyle changes | | | | | | | | | |
| Exercise prescription* | | — | | | — | | | — | |
| Dietary counseling with RD | 47% | 51% | 0.08 | 56% | 56% | 0.95 | 55% | 53% | 0.41 |
| Current smoking | 10% | 14% | 0.02 | 8% | 11% | 0.02 | 8% | 10% | 0.07 |
| Sample size of current smoker at annual visits | | — | | (n = 47) | (n = 165) | | (n = 45) | (n = 146) | |
| Smoking cessation† | | — | | 70% | 74% | 0.61 | 80% | 76% | 0.58 |

Values are %. *The receipt of an exercise prescription from the cardiologist was not routinely documented on the case report form until November 2004. Therefore, there were large numbers of missing data for years 1 and 2. †Smoking cessation counseling was only implemented in current smokers.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; RD = registered dietitian.

pared with *t* test. Longitudinal linear mixed models were built to compare the follow-up health status scores by sex with adjustment for time, randomization strategies, intended revascularization strata, corresponding baseline health status scores, and other baseline characteristics. The interactions between sex and follow-up year and between sex and randomization strategies were tested in each model and dropped if not statistically significant. For the correction of multiple comparisons, the statistical significance level was set at <0.01. Analyses were performed by SAS (version 9.1.3, SAS, Cary, North Carolina). Figures were plotted by R software (R Development Core Team).

## Results

Baseline demographic and clinical variables are depicted in Table 1. Among the 2,368 patients, 702 (29.6%) were women. A larger proportion of women were black. Compared with men, women reported longer durations of diabetes, had a higher prevalence of hypertension, and were less likely to have had a prior MI or to have ever smoked cigarettes. The mean body mass index was higher in women than men, and fewer women than men had an LDL <100 mg/dl (2.6 mmol/l) and a $HbA_{1c}$ <7.0%. A larger percentage of women than men reported angina or angina equivalents. Women were more likely than men to have unstable angina in the 6 weeks preceding enrollment. Among patients with stable symptoms, more women than men had an unfavorable Canadian Cardiovascular Society functional class (class 3 and 4). Women had lower DASI scores and lower scores for Self-Rated Health.

Table 2 depicts the angiographic data stratified by sex. Women had less severe CAD with fewer significant lesions than men, fewer total occlusions, and a lower mean Myocardial Jeopardy Index (MJI). A smaller proportion of women had multiple diseased regions. Moreover, women had better left ventricular function and a lower prevalence of left ventricular dysfunction than men. Physicians more often recommended a PCI procedure for women than for men (74% vs. 65%, $p < 0.01$). However, after adjustment for baseline variables and extent of disease, the choice of PCI compared with CABG was not significantly different (adjusted OR for PCI vs. CABG in women compared with men: 1.22, 99% CI: 0.88 to 1.70, $p = 0.12$).

Table 3 depicts the procedural characteristics by sex for the 765 patients assigned to initial PCI and 347 patients assigned to initial CABG. Procedural results for women and men undergoing PCI were similar, with a similar residual MJI score and a similar number of intended and successfully treated lesions. Women undergoing CABG received fewer grafts than men. After adjusting for baseline variables and extent of disease, there was a borderline significant difference in the number of grafts implanted in women and men during CABG surgery (beta coefficient = −0.29, $p = 0.013$). Residual MJI after CABG was similar in women and men.

Medications prescribed to patients and lifestyle changes that were advised by the healthcare team are depicted in Table 4. Overall, there were no sex differences in the percentage of patients treated with antiplatelet therapies, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, or calcium channel blockers. However, a larger proportion of women than men were treated with non-sublingual nitrates and diuretics. A similar percentage of women and men was given exercise prescriptions, received dietary counseling with a registered

**Table 4 Continued**

| Follow-Up Year | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3-Yr | | | 4-Yr | | | 5-Yr | | |
| Women (n = 569) | Men (n = 1,392) | p Value | Women (n = 498) | Men (n = 1,231) | p Value | Women (n = 318) | Men (n = 759) | p Value |
| 90% | 86% | 0.01 | 88% | 85% | 0.09 | 90% | 87% | 0.15 |
| 38% | 38% | 0.99 | 42% | 37% | 0.07 | 41% | 36% | 0.16 |
| 92% | 91% | 0.37 | 92% | 90% | 0.21 | 89% | 91% | 0.21 |
| 29% | 18% | <0.01 | 28% | 16% | <0.01 | 27% | 15% | <0.01 |
| 75% | 56% | <0.01 | 77% | 57% | <0.01 | 77% | 60% | <0.01 |
| 96% | 96% | 0.63 | 96% | 95% | 0.55 | 94% | 95% | 0.74 |
| 95% | 96% | 0.43 | 95% | 94% | 0.81 | 95% | 94% | 0.57 |
| 71% | 74% | 0.13 | 71% | 73% | 0.38 | 64% | 68% | 0.16 |
| 54% | 51% | 0.28 | 52% | 49% | 0.28 | 42% | 45% | 0.30 |
| 7% (n = 40) | 10% (n = 130) | 0.05 | 7% (n = 35) | 9% (n = 115) | 0.20 | 9% (n = 25) | 9% (n = 68) | 0.71 |
| 98% | 81% | 0.01 | 89% | 82% | 0.34 | 80% | 87% | 0.42 |

dietitian, and was administered treatments for smoking cessation if they continued to smoke. Women were less likely than men to achieve guideline-recommended target goal for LDL <100 mg/dl over the 5 years of follow-up (adjusted OR for achieving an LDL goal of <100 mg/dl in women vs. men: 0.62, 99% CI: 0.50 to 0.77, $p < 0.0001$). The adjusted odds for achieving an $HbA_{1c}$ <7% or a blood pressure ≤130/80 mm Hg over 5 years of follow-up was not significantly different by sex (adjusted OR for achieving an $HbA_{1c}$ goal of <7% in women vs. men: 0.95, 99% CI: 0.76 to 1.19, $p = 0.53$; adjusted OR for achieving a blood pressure ≤130/80 mm Hg in women vs. men: 0.95, 99% CI: 0.79 to 1.14, $p = 0.46$).

The 5-year Kaplan-Meier event rates for the primary endpoints and the principal composite secondary endpoints as well as other clinical outcomes in women and men are depicted in Table 5 and Figure 1. Over 5 years, no sex differences were observed in BARI 2D primary study outcomes, although women were more likely than men to have CHF in follow-up. After adjustment for difference in baseline variables, the hazard of death or death/MI/stroke for women versus men was similar, as were the adjusted rates of subsequent revascularization and CHF.

Angina, DASI, and self-rated health at baseline and at each annual visit are depicted in Figures 2, 3, and 4. A larger percentage of women than men reported angina in follow-up. Women had lower reported scores for DASI and Self-Rated Health. Even after adjusting for baseline status and other confounding variables, women were more likely than men to report angina (adjusted OR: 1.51; 99% CI: 1.21 to 1.89, $p < 0.0001$), and women had significantly lower DASI scores than men (adjusted beta coefficient: −1.58, 99% CI: −2.84 to −0.32, $p < 0.01$). After adjustment, self-rated health was not significantly different between women and men (adjusted beta coefficient: 0.32, 99% CI: −2.4 to 1.7, $p < 0.7$).

**Table 5 Clinical Outcomes in Women and Men**

| | 5-Yr Cumulative Event Rate | | | Adjusted* HR Women vs. Men | |
|---|---|---|---|---|---|
| Outcomes | Women | Men | p Value | HR (99% CI) | p Value |
| Death | 11% | 12% | 0.45 | 0.91 (0.63–1.32) | 0.53 |
| Death/MI/CVA | 26% | 22% | 0.12 | 1.11 (0.85–1.44) | 0.34 |
| Subsequent revascularization | 35% | 32% | 0.24 | 1.04 (0.82–1.31) | 0.69 |
| CHF | 20% | 16% | <0.01 | 1.19 (0.87–1.63) | 0.15 |

*Adjusted for randomized treatment strategies (revascularization vs. medical therapy, and insulin provision vs. insulin sensitization), pre-specified strata (PCI vs. CABG), age at entry, race ethnicity, United States versus other countries, baseline characteristics including: MI, hypertension, angina, duration of DM, taking insulin at baseline, smoking status, disease myocardial region, totally occluded region, and abnormal LVEF (<50%).

CI = confidence interval; CVA = cerebrovascular accident; HR = hazard ratio; other abbreviations as in Tables 1, 2, and 3.

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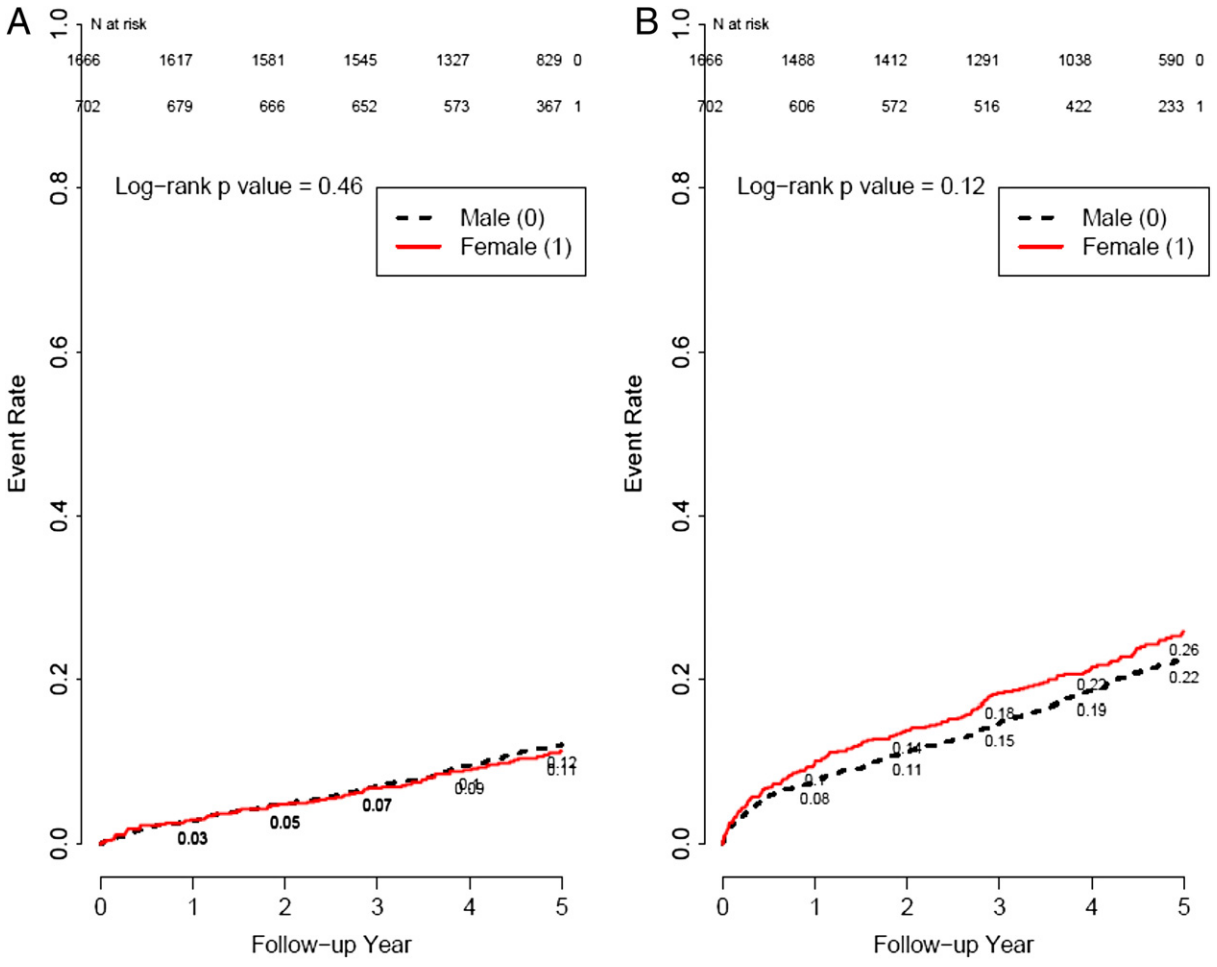


**Figure 1** **5-Year Cumulative Event Rates in Women and Men**

The 5-year cumulative rate of death **(A)**; and the combined endpoints of death, myocardial infarction, and cerebrovascular accident **(B)** in women and men.

## Discussion

In the current study, we analyzed the clinical presentation and outcome of women and men enrolled in the BARI 2D trial. The protocol-mandated trial design resulted in similar management of women and men, including recommendations with regard to lifestyle changes, medical therapies, and revascularization. When considering revascularization options, doctors advised a similar approach for women and men, with comparable rates of PCI versus CABG after adjusting for differences in baseline angiographic data and other clinical variables. There were no sex differences in procedural success for PCI, including the number of intended and revascularized lesions and residual MJI. Women undergoing CABG received fewer bypass grafts than men. This was probably related to the less extensive and severe disease reported at baseline in women; after adjusting for baseline variables and extent of disease, this difference was borderline significant. Despite this, success of revascularization, defined by residual MJI, was similar for women and men after CABG. Women were more likely than men to be prescribed non-sublingual nitrates and diuretics. Otherwise, therapies for treatment of CAD were similar by sex. As one might expect, given the very similar and intensive management of CAD and DM in our patients, clinical outcomes were equivalent between women and men, including mortality and the combined endpoints of death, MI, and CVA at 5 years of follow-up. This implies that the difference in outcome between women and men reported in prior studies might have been partly a result of sex-based differences in management.

Despite the similarities in management, women remained more symptomatic then men with more angina and poorer functional status as assessed with the DASI questionnaire. These differences were noted even after adjusting for other confounding variables. However, women and men had equal adjusted scores for Self-Rated Health in follow-up. Our study supports earlier reports that have demonstrated poorer QOL (16,23–26) and more angina (5,11,12,16,23,27) in

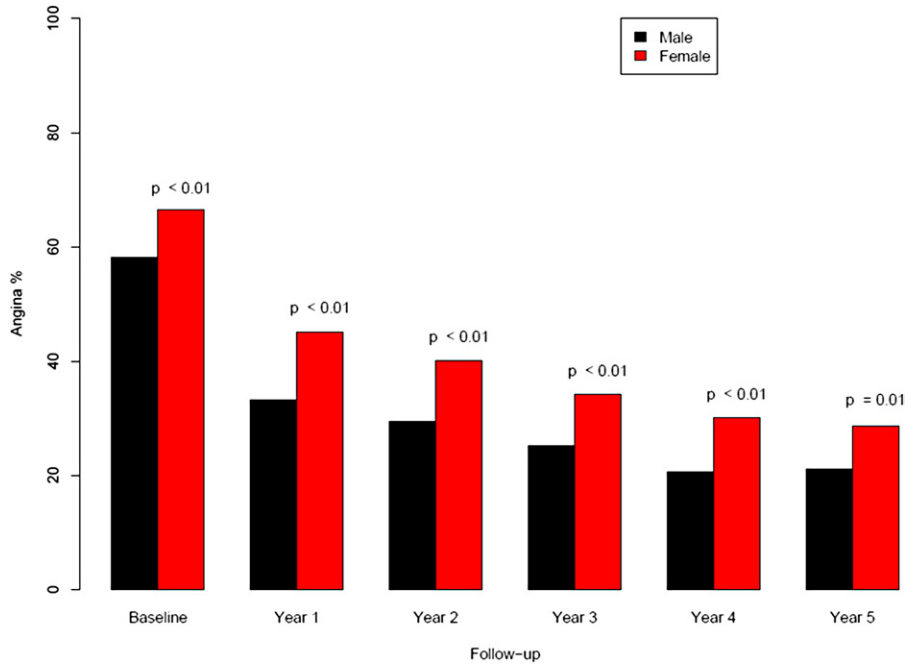


**Figure 2** **Angina Prevalence in Women and Men**

Prevalence of angina in women and men at each yearly follow-up visit.

women with CAD when compared with men. However, unlike prior studies, the BARI 2D protocol allowed us to analyze symptoms between women and men who received intensive and highly regulated therapies for management of CAD and DM; the extent of regulation and treatment that study participants received in BARI 2D is not often achieved in the "real world." It is interesting to note that, even though a similar percentage of women and men were treated with statin therapy, women were less likely than men to achieve the guideline-recommended target goal for LDL <100 mg/dl. Although this finding is potentially interesting, it is unlikely that this would explain the poorer functional status or higher rates of angina in women.

Physical functioning is a complex variable that is influenced by multiple co-existing conditions, including baseline functional status, the severity of the heart disease of a patient, the presence of other comorbid illnesses (including diastolic dysfunction, underlying lung disease, obesity, degenerative joint diseases, or prior CVA), and psychosocial barriers. In the current analysis, we attempted to examine QOL by DASI scores, after adjusting for other variables that might have impacted on physical functioning; however, it is possible that certain "unmeasured" variables (degenerative joint disease, lung disease, depression, and social support) might have contributed to a poorer functional status in the women studied when compared with men.

Physical functioning is also affected by psychosocial factors, including depression, anxiety, and social support (28). Women with CAD experience more depression than men and have less social support (16,23). In a large prospective study of women and men with CAD (16), functional status was found to be significantly lower in women than men. In this study (16), women had higher rates of depression and less social support; these variables were shown to have a negative impact on functional status. These data suggest that inadequate social support and depression might adversely affect functional status, and therefore, acquisition of a broader psycho-social history might be necessary when evaluating patients with CAD. It is possible that a more aggressive approach to the assessment and management of physical and psychosocial barriers in patients with CAD (including referral to structured cardiac rehabilitation programs, depression screening and treatment, and programs designed to aid in social support) might contribute to an improvement in functional status in women.

The degree to which a patient might experience angina is dependent on multiple conditions, including the severity of atherosclerotic CAD (or residual myocardium in jeopardy), myocardial oxygen demand, the presence of microvascular disease, the use of anti-anginal medications, the degree of baseline angina, and patient perception of pain; all of these factors might contribute to symptom presentation to a different degree in women and men. Our multivariate analysis adjusted for differences in baseline symptoms, clinical data, angiographic variables, and choice of revascularization. Yet, women still had more angina than men. In

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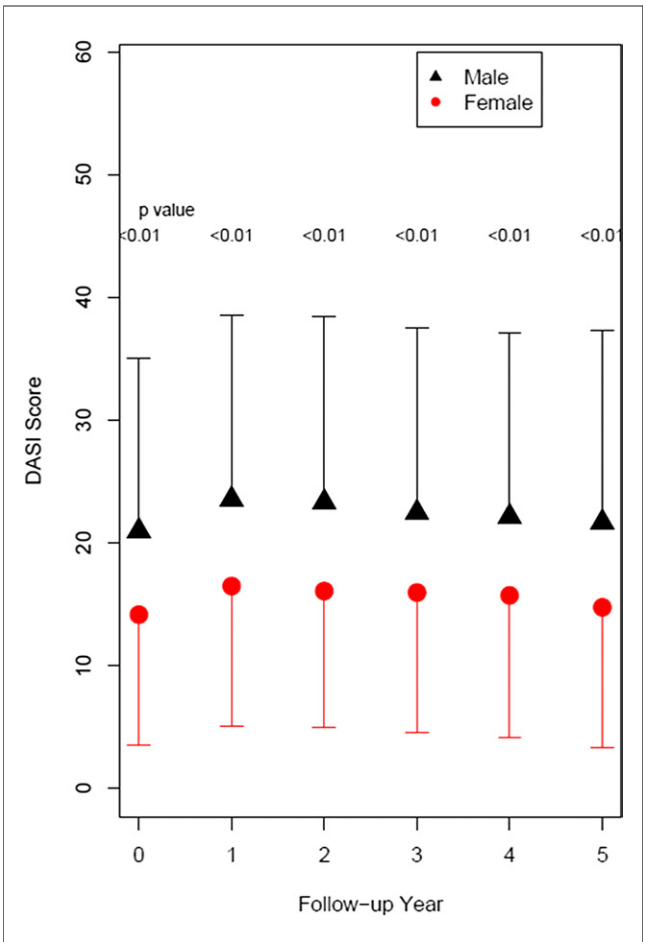


**Figure 3** Duke Activity Status Index in Women and Men

Scores recorded for the Duke Activity Status Index (DASI) in women and men at each yearly follow-up visit.

follow-up, there seemed to be comparable cardiovascular disease-focused management of enrolled women and men, including the approach to revascularization (for those patients randomized to revascularization), procedural success after revascularization, and medical therapies used for the treatment of angina. In fact, women were actually prescribed anti-anginal medications more often than men. Therefore, the differences we reported in rates of angina in women and men were unlikely to be a result of differences in therapies administered. It is not clear whether the higher prevalence of angina in women reflects true ischemia related to microvascular disease or a lowered symptom threshold in women.

It is interesting to note that, at baseline, women had more significant angina than men, despite the less extensive disease noted on coronary angiography. This has been reported in prior studies (1). Endothelial dysfunction or microvascular disease is a syndrome characterized by abnormalities in vascular homeostasis and vasomotor tone, resulting in ischemic-like symptoms and increased risk for cardiovascular events. Syndrome X, which is defined as typical angina in the setting of normal coronary angiograms, has been attributed in part to endothelial dysfunction (29) and is more common in women (30).

Some studies have demonstrated sex differences in somatic pain perception and pain thresholds, with a lower pain threshold in women and a lower tolerance for pain (31) compared with men. However, other reports have suggested that, among patients with physical conditions, women are less likely to report symptoms than men (32). In our study, although functional status was poorer and angina was more frequent in women than men, women and men had comparable scores for self-rated health. If "perception of symptoms" related to health status was the reason for the lower functional scores in women and the higher rates of angina, one would expect that self-rated health would also be lower in women than men. Yet, this was not noted. This implies that the "perception of symptoms" of a woman related to health status were less likely to be responsible for the differences we noted in our study.

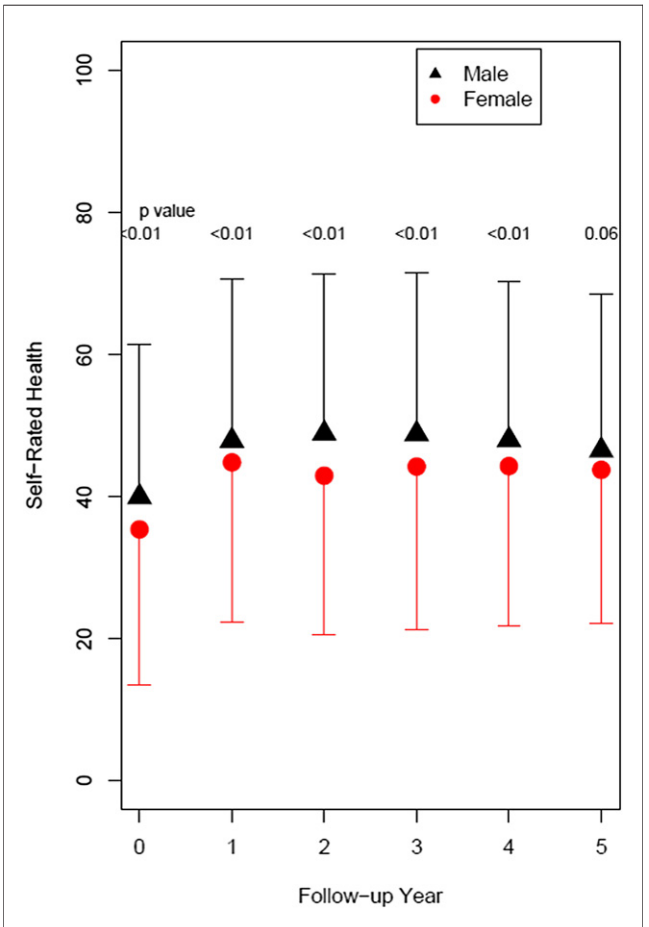


**Figure 4** Self-Rated Health in Women and Men

Scores recorded for Self-Rated Health in women and men at each yearly follow-up visit.

**Study limitations.** The BARI 2D study assessed a specific population of patients with type 2 DM and stable CAD amenable to revascularization. Because the BARI 2D trial only enrolled patients with stabilized CAD and symptoms appropriate for treatment with either medical therapy or revascularization, it is possible that we excluded patients with more extensive disease or more severe symptoms requiring earlier intervention where more pronounced sex differences might be observed. Social support and depression were not routinely measured in our patients; therefore the degree to which these variables impacted the differences in QOL and symptomatic angina could not be assessed. Finally, although angina was routinely assessed at each visit, a standardized questionnaire such as the Seattle Angina Questionnaire was not administered.

## Conclusions

Women and men with type 2 DM and CAD enrolled in the BARI 2D trial received very similar management strategies and had a similar incidence of cardiovascular events over the 5-year period of follow-up. Despite these similarities, women remained more symptomatic than men, with more angina and persistence of lower functional status even after adjustment for baseline variables and therapies administered. Our findings offer important insight into the clinical care of patients with DM and stable CAD. In women with established CAD, consideration should be given to more aggressive therapies aimed at treatment of angina and individually prescribed physical activity programs aimed at improvement in functional capacity.

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**Key Words:** angina ■ coronary artery disease ■ diabetes ■ quality of life ■ sex.